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How Different Wavelengths of the Ultraviolet Spectrum Contribute to Skin Carcinogenesis: The Role of Cellular Damage Responses

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The carcinogenic properties of ultraviolet (UV) light are mediated by its ability to generate DNA damage. Cellular responses to UV-induced DNA damage profoundly modulate the carcinogenic effects of UV exposures, and these responses are wavelength dependent. However, the exact contributions of different wavelengths of UV light to DNA damage, cellular damage responses, mutation, and skin carcinogenesis are incompletely understood. Given that UV-induced apoptosis is a protective cellular response to UV that prevents survival of damaged cells, inhibition of UVB-induced apoptosis by adding UVA, as reported by Ibuki *et al*. in this issue, may be a mechanism by which UVA augments UVB-mediated mutation and skin cancer formation.

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Photocarcinogenesis is most commonly thought to be the result of a chain of events that involve formation of DNA damage and subsequent mutation formation following exposure to ultraviolet light (UV) (Figure 1) (Rünger, 2003). Several cellular defense mechanisms reduce the likelihood that one occurrence in this cascade leads to the next (Figure 1). Many of these protective responses can be induced by UV, thereby providing additional protection against subsequent exposures. All of these responses are mediated by a tightly controlled network of signaling pathways, many of which involve the tumor suppressor p53. UV-induced mutations of p53 with subsequent disruption of cellular damage responses are a hallmark of most sun-induced cutaneous squamous-cell carcinomas (Brash *et al*., 1996). This further underlines the importance of these damage responses for the prevention of photocarcinogenesis.

The melanin microparasol that covers the nucleus of basal keratinocytes reduces formation of DNA damage with exposure of the skin to UV. Once DNA damage is formed, most of it is repaired and does not give rise to mutations. This is exemplified by the genodermatosis xeroderma pigmentosum, in which the relative inability to repair UV-induced DNA damage results in UV hypermutability in cells and an increased frequency of skin cancers in UV-exposed areas of affected patients. Another mechanism that

> UVA radiation inhibits UVB-induced apoptosis in mouse epidermal cells.

inhibits mutation formation at sites of DNA damage is a G1/S cell–cycle arrest that prevents cells from replicating damaged DNA, a situation particularly prone to the introduction of mutations (Decraene *et al*., 2001). DNA polymerase η, which is mutated in xeroderma pigmentosum variant, is a translesion DNA polymerase spe-

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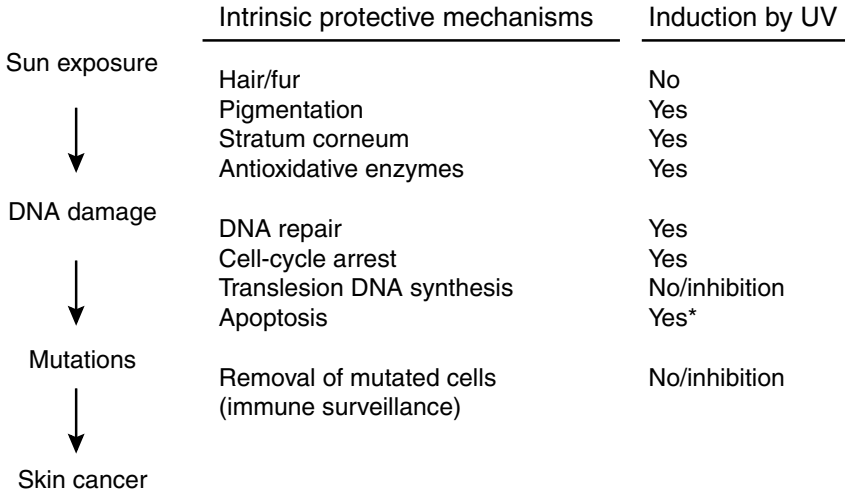

Figure 1. The photocarcinogenesis chain of events and intrinsic protective mechanisms for the prevention of skin cancer formation following sun exposure. *Although UVB readily induces apoptosis, adding UVA inhibits UVB-induced apoptosis, as reported in this issue by Ibuki *et al*. (2007).

cialized to bypass DNA photoproducts. It is downregulated through (UV-induced) activation of p53, which maintains a low mutagenic activity at the price of a reduced damage bypass (Avkin *et al*., 2006). Activation of damage response signaling pathways often results in apoptosis of UV-irradiated cells. This prevents survival of cells with overwhelming DNA damage and thereby prevents the rise of cells with UV-induced mutations. Even after mutations have been established, most of these cells will be removed by immune-mediated cell killing. This immune surveillance plays an important role in the prevention of cancer formation. However, it is inhibited in the skin by sun exposure.

The relative contributions of different wavelengths of the solar UV spectrum—in particular UVA (315–400 nm) and UVB (280–315 nm)—to these UV-induced cellular events (DNA damage, damage responses, mutation formation, and carcinogenesis) are only incompletely understood. We recently published a spectrum of UVA- and UVB-induced mutations for the first time in non-immortalized, normal human skin cells (Kappes *et al*., 2006). Because UVA is only a weak generator of DNA photoproducts (cyclobutane pyrimidine dimers and 6,4-photoproducts), we were surprised to find that UVA induced a very similar spectrum of mutations as compared with UVB, demonstrating that DNA photoproducts are the main type of premutagenic DNA damage, not only with UVB but also with UVA. Attempting to explain a higher mutation rate per photoproduct with UVA, which according to our results is not explainable by a different type of DNA damage, we hypothesized that UVA induces more mutations at sites of DNA damage than UVB, because it induces only a weaker protective DNA damage response (Kappes *et al*., 2006; Rünger and Kappes, in the press). Indeed, we found a much weaker and shorter-lived activation of p53 by UVA as compared with UVB.

Ibuki *et al*. (2007, this issue) provide compelling evidence that adding increasing doses of UVA (67, 110, and 168 kJ/m^2) to a constant very high dose of UVB (3780 J/m^2) decreases epidermal apoptosis in an *in vivo* mouse model, as shown by a decreased number of sunburn cells and caspase-3-positive cells and less apoptotic DNA fragmentation. The relevance of these data for photocarcinogenesis can be interpreted in two ways. First, as favored by Ibuki *et al*., a decrease in the number of sunburn cells could reflect reduced formation of DNA damage. However, a reduction in DNA damage formation by adding UVA to UVB was not shown, and it is difficult to imagine how adding a DNA damaging agent to another one could result in less damage.

The second way to project effects of the phenomenon described by Ibuki *et al*. on photocarcinogenesis is to understand, as outlined above, apoptosis as a protective, antimutagenic, and anticarcinogenic cellular response. With this understanding, inhibition of apoptosis would be expected to increase mutation burden and, ultimately, skin cancer rates. It will be interesting to see which of the two projections will be confirmed, because Ibuki *et al*. are apparently undertaking such experiments at this time.

The influence of UVA on UVB/UVA skin carcinogenesis in mice has already been studied, albeit not with exactly the same experimental setup as that used by Ibuki *et al*. UVA irradiation augmented the carcinogenic effects of mixed UVB/UVA in two studies (Staberg *et al*., 1983; Willis *et al*., 1981) and diminished or had no effect in two other studies (Forbes *et al*., 1978; Bech-Thomsen *et al*., 1994). In one of the latter two studies (Bech-Thomsen *et al*., 1994), a diminished rate of UVB-induced tumors was observed with low doses, but not with a higher dose of UVA.

To expand our hypothesis (see above), UVA not only appears to induce a weaker DNA damage response than UVB but may even inhibit it. For practical applications, this would mean that UVA protection is indeed very important for the prevention of photocarcinogenesis. The speculation by Ibuki *et al*. that UVA may be used for protection against the photocarcinogenic properties of UVB may be interesting, because it is provocative and questions current thinking. However, much more evidence is required to change current recommendations for UVA photoprotection.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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